April 25, 2006

N. Bhushan Mandava, Ph.D.
Technical Contact
Huntsman-Nissan TGIC Consortium
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Suite 906
Washington, DC 20036

Dear Dr. Mandava:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Triglycidyl Isocyanurate posted on the ChemRTK HPV Challenge Program Web site on January 19, 2005 I commend the Huntsman-Nissan TGIC Consortium for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Consortium advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Triglycidyl Isocyanurate

Summary of EPA Comments

The sponsor, the Huntsman-Nissan-TGIC Consortium, submitted a test plan and robust summaries to EPA for Triglycidyl isocyanurate, (TGIC;1,3,5-tris(2,3-epoxypropyl)-S-triazine-2,4,6(1H,3H,5H)-trione; CAS No. 2451-62-9) dated December 27, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 19, 2005.

EPA has reviewed this submission and has reached the following conclusions:

1. Substance Identity. The test plan needs to address the issue of isomers that is touched upon in one of the robust summaries.

2. Physicochemical Properties. The submitter needs to provide clarifications for boiling point, vapor pressure, and partition coefficient and additional information on melting point.

3. Environmental Fate. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program.

4. Health Effects. The submitted data are adequate for the acute, repeated-dose, and genetic toxicity endpoints; the submitter needs to provide reproductive and developmental toxicity data. Deficiencies in the robust summaries need to be addressed.

5. Ecological Effects. The submitted data are adequate for all endpoints. The submitter needs to address some missing data elements in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Triglycidyl Isocyanurate Challenge Submission

Test Plan

Substance Identity

The robust summary for water solubility mentions the existence of the stereoisomers α-TGIC and β-TGIC, but this is not discussed elsewhere in the submission. The test plan needs to describe the isomers, their occurrence in the commercial substance, and whether and how their different physicochemical properties may be relevant to any of the SIDS endpoints (see also melting point and boiling point sections below).

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The melting point and water solubility data provided by the submitter are adequate for the purposes of the HPV Challenge Program.

Melting point. The submitter needs to include information in the robust summary, similar to that for water solubility, on the stereoisomers α-TGIC (m.p. 105 °C) and β-TGIC (m.p. 156 °C)(data from Nordic Expert Group reference), their occurrence in the commercial substance, and their significance for this endpoint, and cite the source of the information. While the summary does not mention decomposition during melting, the boiling point summary states that TGIC decomposes at its melting point; if true, the melting point summary needs to reflect this.

Boiling point. The submitter noted in the test plan summary table that adequate data are available for this endpoint. On page 5 of the test plan, the submitter provided a boiling point of 300 °C (decomposes) for TGIC. However, in the robust summaries, the submitter stated that a boiling point could not be determined because TGIC decomposes at its melting point (95 °C in the robust summary). The submitter needs to address this discrepancy and provide a correct decomposition temperature. In addition, to the extent that the α- and β-stereoisomers are relevant to the interpretation of this endpoint, such discussion should be added to the summary (see *Melting point*, above).

Vapor pressure. The vapor pressure value (0.00072 Pa at 20 °C or 7.2 $x10^{-7}$ KPa), although adequate, differs from another value of 7.2$x10^{-9}$ KPa (5.4$x10^{-8}$ mm Hg) at 20 °C (Nordic Expert Group reference). The submitter needs to address the apparent discrepancy.

Partition coefficient. The submitter provided a log Pow of 0.80 at 95 °C in the robust summaries for TGIC, but in the test plan reports a log Pow of -0.8. The submitter needs to address this discrepancy.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data are adequate for the acute, repeated-dose, and genetic toxicity endpoints. The submitter needs to address missing study details in the robust summaries.

Reproductive/developmental toxicity. EPA considers the data submitted for the reproductive toxicity endpoint inadequate because the studies only examined males. Although the submitter claims a lack of findings for reproductive effects in the13-week study (page 170), this and other available studies indicate toxicity of TGIC to sperm, spermatids and spermatogonia. In addition, the Test Plan (page 29) reports that lowered weights of ovaries, uterus, prostate, and seminal vesicles were recorded in a 19-day oral study of TGIC. These results underline the need for adequate reproductive toxicity testing.

No data were presented for studies of developmental toxicity. The discussion presented by the submitter and the available studies are not adequate to address the developmental toxicity endpoint, given the absence of studies on female reproductive toxicity and the observed effects on male reproductive tissues.

The submitter needs to provide data for the reproductive and developmental toxicity endpoints. EPA recommends a combined reproductive and developmental toxicity screening test (OECD TG 421).cological Effects (fish, invertebrates, and algae)

Adequate data exist for all endpoints; however, the submitter needs to provide the missing study details.

Invertebrates. The test plan (pages 6 and 42) incorrectly reports the *Daphnia magna* LC_{50} value as >77 mg/L; according to the robust summary, the EC_{50} value (based on measured concentrations) is 90.6 mg/L.

Specific Comments on the Robust Summaries

Generic Comments

In each robust summary, the submitter needs to state the percentage purity of the test substance used in the study.

Health Effects

Repeated-dose toxicity. The robust summary for the 13-week oral toxicity study in male rats (page 154) is missing details including statistical methods and results of statistical analyses, clinical parameters examined and results, a list of tissues and organs examined at necropsy and in histopathology, results of necropsy and histopathology, the number of animals dead or moribund at each dose level, and the number of animals with lowered leukocyte and lymphocyte counts at each dose level.

Genetic toxicity (Gene mutations). The robust summary for the mutagenicity test on ARALDITE PT 810 in the Ames Salmonella/Microsome Reverse Mutation Assay (page 132) is missing details including the criteria for a positive response, individual plate counts, mean number of revertants/plate, and magnitude of increased revertants. This robust summary lists as the "Method/Guideline Followed" three FDA and EPA regulations from the Code of Federal Regulations which are Good Laboratory Practice Standards, not test guidelines.

Four robust summaries for mutagenicity tests on Tepic-G in the Ames assay using *Salmonella typhimurium* and *Escherichia coli* are missing details including criteria for a positive response, dose-response information, information on control responses, and details of cytotoxicity.

Genetic toxicity (Chromosomal aberrations). The robust summary for the "Study to Evaluate the Chromosome Damaging Potential of TK 10622 PT 810 (TGIC 97%)" (page 102) is missing details on the frequency of aberrations at each dose level and on the toxicity of the test material.

The robust summary for the chromosome analysis in mouse spermatogonial cells following inhalation of TGIC Technical and TGIC 10% Powder (page 99) is missing details on the criteria for a positive response, frequency of aberrations in each test group, and part of the statistical analyses results (Chi-squared Test and One-Way ANOVA). The robust summary reports conflicting results by stating in the results section that the total aberrations achieved statistical significance at $p < 0.01$, and that the genotoxic effect was negative, and in the conclusions section that the response was equivocal in terms of chromosome aberrations. The submitter needs to clarify the results of this study and provide the missing details.

Reproductive toxicity. For the 13-week oral repeated-dose toxicity study, missing details include a list of reproductive organs examined in necropsy and histopathology, the results of those examinations, and results of observed reproductive toxicity including fertility, gestation, and viability indices.

Developmental toxicity. The robust summary references listed appear misplaced.

Ecological Effects

Fish. The following missing data elements need to be included: fish mortality and/or effects observed at the tested concentration, water hardness, dissolved oxygen content, and pH.

Invertebrates. The following missing data elements need to be included: water hardness, dissolved oxygen content, mortality and/or effects seen at each test concentration, and the EC50 value based on measured concentrations.

Algae. The following missing data elements need to be included: details on cell density at each test concentration, water hardness, and pH.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.